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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/432,503	11/02/1999	THOMAS R. CECH	15389-002611	1130

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/432,503	CECH ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-62 and 65-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *41-57 and 74-82* is/are allowed.

6)☒ Claim(s) *58-62 and 65-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/05 has been entered.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 41-62 and 65-82 are currently pending and are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-62 and 65-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of increasing the proliferative capacity of a cell as indicated in the claims wherein the cell is in vitro;

does not reasonably provide enablement for therapeutic methods of increasing the proliferative capacity of a cell wherein the cell is in vivo, for the reasons of record set forth in the previous Office Action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Given the broadest reasonable interpretation, the nature of the invention is biomedical therapy and includes gene therapy for treating humans having disease or disorder.

The breadth of the claims

As indicated above, the claims are very broad and encompass methods for increasing the proliferative capacity of mammalian cell by administering to the cell a polynucleotide that encodes a polypeptide that has telomerase catalytic activity when complexed with a telomerase RNA. A careful reading of the claim language also reveals that the claim does not explicitly require that the target mammalian cell have the Telomerase RNA required for TRT catalytic

activity. Claims 58-91 encompass the method wherein the mammalian cell is in vivo. With respect to the in vivo embodiments of the claims, it is respectfully pointed out that the only contemplated use for the method described in the specification is for treating disease/disorder. As such, the only contemplated use for the method is for gene therapy to treat a disease/disorder. With respect to treating a disease/disorder, it is respectfully pointed out that the claims are not limited to treating any particular specific disease and the specification specifically contemplates treating a vast array of different diseases including: cancer, Alzheimer's disease, Parkinson's disease, stroke, graying of hair, hair loss, wound healing, osteoporosis, age-related immune system impairment, atherosclerosis, diabetes, muscle atrophy, etc. (e.g., see p. 98-100). Furthermore, the claims do not specifically indicate how the polynucleotide is delivered to the cells; therefore, the claims embrace any type of administration/delivery of the therapeutic molecule. Therefore, given the broadest reasonable interpretation of the claims, the claims encompass a method for treating any disease/disorder using the claimed method by any means of administration.

The unpredictability of the art and the state of the prior art

With respect to claims as they read on administering a polynucleotide comprising a sequence encoding a catalytically active TRT, one of skill in the art would be fully aware that in order for the polynucleotide to express the encoded polypeptide in a cell, the sequence encoding the polypeptide must be operably linked to transcriptional control elements (such as promoter/enhancer elements). If the polynucleotide sequence is not operably linked to transcriptional control elements, then one of skill in the art would not expect the sequence to be expressed.

With respect to the claims as they encompass administering the polynucleotide to cells that do not comprise Telomerase RNA, it is respectfully pointed out that the specification indicates that the activity of TRT requires the presence of the Telomerase RNA (TR) to function as a template for initiating the catalytic activity of TRT. Therefore, one of skill in the art would recognize that in order for the claimed method to work, the target cell must comprise the required telomerase RNA.

With respect to the claims as they encompass in vivo embodiments (as indicated above) the claims encompass gene therapy for treating disease. Regarding gene therapy as a whole, the art at the time of filing considered gene therapy to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, ANDERSON (Nature 392(Suppl):25-30; 1998) teaches,

> "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease (p.25, first paragraph)... The challenge is to develop gene therapy as an efficient and safe drug-delivery system. The goal is more difficult to achieve than many investigators had predicted 5 years ago. (p. 25 , second paragraph)... Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome and how to manufacture efficiently the vectors we do make."(See p. 30).

With respect to using TRT for gene therapy, the relevant art indicates that there are a number of problems that must be overcome in order for TRT gene therapy to be considered predictable. For instance, HORNSBY et al. (J. Anti-Aging Med, 2000) teaches,

> "The use of telomerized cells depends on expression of (hTRT) not causing changes that predispose cells to abnormalities of any kind, particularly neoplastic conversion. Since the initial reports of telomerization, conflicting data have been presented with respect to risks of abnormalities in cells that have been telomerized... The data that have been obtained so far do not unequivocally show the (hTRT) is able to immortalize cells without the production of any abnormalities... Other data, in fact, suggest that immortalization by (hTRT) could predispose cells to neoplastic transformation. Most significant is the finding that expression of (hTRT) is required for full tumorigenicity in human cells also expressing mutated Ras and large T/small t antigens from SV40.:. Considering the available data, we cannot yet predict whether telomerized cells transplanted into a host animal do in fact present a cancer risk; this can only be determined directly by long-term observation, and this has not yet been done." (See p. 412)

HORNSBY also teaches,

> "The future prospects for the use of telomerized cells are significant. As emphasized here, major efforts need to be made to be sure that telomerization is safe when applied to cells for use in human therapy." (See p.416)

OSTLER et al. (J. Ped. Endocrin. & Metab., 2000) teaches that telomerase (hTRT) has been shown to halt telomere shortening and is sufficient to prevent senescence in at least three human cell types (fibroblasts, vascular endothelial cells and retinal pigmented cells) conferring first extended life span and then formal immortality (e.g., see last paragraph p. 1472).

Regarding telomere-driven senescence mechanisms in other mammals, OSTLER teaches,

> "It is unlikely, however, that this [telomere-driven senescence] mechanism operated in rodent species. Rodents have much greater mean telomere lengths than humans, a significant spontaneous escape frequency from senescence (10-6/cell/generation compared with 10-12/cell/generation in humans) and (more seriously) some rodent fibroblasts have been shown to undergo senescence in the presence of active telomerase." (See p. 1473, first paragraph).

Regarding the possible use of Telomerase for therapeutic purposes, OSTLER teaches,

> "There is considerable popular interest in the potential application of telomerase to tissue engineering and anti-aging therapies. Leaving aside the practical difficulties of the safe use of telomerase, it is clear that ectopic expression of the enzyme (or even transient telomerase reactivation) should not be treated as a 'one size fits all' intervention for compromised replicative capacity in every tissue." (See p. 1474).

Therefore, it is clear that the relevant art recognizes that treating diseases that are contemplated by the specification is harder than merely increasing the proliferation of cells associated with the disease and a number of different factors have to also be considered and addressed before TRT gene therapy can be considered a predictable art.

Working Examples and Guidance in the Specification

The specification shows the nucleic acid (and amino acid) sequences that encode a few different TRT genes from different species, and indicates the potentially conserved homologous domains of the different TRTs (e.g., see Fig. 4). The specification also shows that expression of hTRT in different cells types, wherein the cells are in vitro (e.g., see Fig. 5 and Example 2). The specification also shows that the co-expression of hTRT and hTR are required for telomerase catalytic activity in a cell, in vitro (that is, both TRT and the Telomerase RNA are required) (e.g., see Fig. 10). The specification, however, does not have any working examples wherein the target cells are in vivo. Furthermore, the specification does not show how the polynucleotide encoding the TRT can be administered to the correct target cell in vivo, and how to avoid transformation of non-target cells in vivo. The specification does not indicate any specific functional variants or fragments of hTRT that can be used in the claimed method. The specification does disclose that deleting certain specific domains of the polypeptide eliminates the catalytic activity of the protein, but there is no evidence presented indicating that any specific

fragment or variant of hTRT (i.e. SEQ ID NO: 2) has catalytic activity when expressed in a cell. The specification also does not offer any guidance with respect to expressing the catalytic molecule in a cell wherein the polynucleotide encoding the catalytic molecule is not operably linked to expression control elements (such as in a vector).

Quantity of Experimentation

Considering the vast breadth of the claims, an enormous amount of additional experimentation would be required in order for one of skill in the art to be able to predictably use the claimed invention to its full scope. For instance, additional experimentation would be required in order to be able to use the claimed method to treat a mammal having a disease/disorder. Considering the problems recognized in the art at the time of filing and in the post-filing art (indicated above), it is clear that the additional experimentation would not be a matter of "routine experimentation". Furthermore, the evidence presented in the instant specification (e.g., see Fig 10) indicates that in order to produce a telomerase catalytic activity in a cell both the TRT and TR genes must be expressed in the cells (i.e., the cells must have both the telomerase enzyme and the telomerase RNA unit). However, the claims do not explicitly indicate that the target cell expresses both TRT and TR. Therefore, additional experimentation would be required in order to be able to practice the claimed method in a cell that does not express TR. Again, this would not be a matter of routine experimentation. Furthermore, the claims do not explicitly indicate that the polynucleotide encoding the telomerase polypeptide is operably linked to transcriptional control elements (such as a vector). Since one of skill in the art would be aware that this was required to properly express the recombinant gene in a cell, additional experimentation would be required.

Level of the skill in the art

The level of the skill in the art is deemed to be high, considering the complex nature of biomedical therapy.

Conclusion

Considering that the claims are extremely broad such that they encompass methods that can be performed either in vitro or in vivo, and considering that the in vivo embodiments of the claims encompass treating a vast number and different types of diseases wherein the mere increasing of the proliferation of the cells associated with the disease would not be expected to result in treatment of the disease, the claims are not enabled to the full scope that they embrace. That is, considering the nature of the invention (gene therapy) and the vast breadth of the claims (treating any disease via any type of administration) in view of the teaching in the art that gene therapy is unpredictable and in view of the limited working examples and guidance provided at the time filing, as well as the high degree of skill required to practice the claimed invention, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Amendment/Arguments

Applicant's arguments filed 12/24/12/22/2005 have been fully considered but are not persuasive.

Applicants indicate that that a supplemental amendment will be filed presenting new claim wording and a new section 1.132 Declaration. However, as of 3/20/06 no supplemental amendment has been received by the Office and due to time constraints, the Examiner could not wait any longer for the Supplemental Amendment.

Applicants assert that the amendment to the claims address the points made in the last office action under 35 USC 112, 1st paragraph.

In response, the instant claims were rejected under 35 USC 112, 1st paragraph for not being enabled for the full scope encompassed by the claims. Specifically, as previously indicated, the instant claims encompass increasing the proliferative capacity of a cell wherein the cell may be either in vitro or in vivo. To the extent that the claims read on increasing the proliferative capacity of a cell in vivo, it was noted that the methods read on therapeutic methods (as previously indicated and reiterated above). The amendment filed 12/22/2005 does not overcome the problems recognized in the art with respect to therapeutic methods of increasing the proliferative capacity of a cell in vivo. Therefore, the amendment and applicants' arguments are not sufficient to overcome the rejection of record. As such, the rejection of the instant claims is not withdrawn.

Allowable Subject Matter

Claims 41-57 and 74-82 are allowed.

Conclusion

Claims 58-62 and 65-73 stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON ANGELL
PATENT EXAMINER